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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. 02P–0391 and 02P–0404]

Determination That Brimonidine Tartrate Ophthalmic Solution 0.2% Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that Alphagan 0.2% (brimonidine tartrate ophthalmic solution) was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for brimonidine tartrate ophthalmic solution 0.2%.

FOR FURTHER INFORMATION CONTACT: Aileen H. Ciampa, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved under a new drug application (NDA). Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain

approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products with Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

Alphagan 0.2% (brimonidine tartrate ophthalmic solution) is the subject of NDA 20–613, held by Allergan, Inc. (Allergan). Alphagan 0.2% is administered as an eye drop to lower intraocular pressure in patients with open-angle glaucoma or ocular hypertension. FDA approved NDA 20–613 on September 6, 1996. In a letter dated August 20, 2002, Allergan informed FDA that it was withdrawing Alphagan 0.2% from the market. In a letter dated September 6, 2002, Allergan clarified that it was not requesting that approval be withdrawn for NDA 20–613, nor was Alphagan 0.2% being recalled from the market. Instead, Allergan explained that it was in the process of discontinuing distribution of Alphagan 0.2%. Following receipt of Allergan's

letters, the agency moved Alphagan 0.2% from the "Prescription Drug Product List" section to the "Discontinued Drug Product List" section of the Orange Book.

In citizen petitions submitted under 21 CFR 10.30 and dated August 27, 2002 (Docket No. 02P–0404/CP1), and August 30, 2002 (Docket No. 02P–0391/CP1), respectively, Alcon, Inc. (Alcon), and IVAX Pharmaceuticals, Inc. (IVAX), requested that the agency determine whether brimonidine tartrate ophthalmic solution 0.2% was withdrawn from sale for reasons of safety or effectiveness. On October 28, 2002, Allergan submitted a citizen petition (Docket No. 02P–0469/CP1) opposing the granting of Alcon's and IVAX's petitions. Comments were submitted in response to Allergan's petition on November 13, 2002, and December 5, 2002, by Alcon and Bausch & Lomb, Inc. (Bausch & Lomb), respectively. Allergan responded to the comments on January 23, 2003. Bausch & Lomb submitted additional comments on February 10, 2003, and Allergan responded on March 18, 2003.

FDA has considered the information contained in the citizen petitions, comments, and agency records and has determined that Alphagan 0.2% was not withdrawn from sale for reasons of safety or effectiveness. There are several grounds for FDA's finding. First, Alphagan 0.2% has a safety and effectiveness profile that is comparable to that of Alphagan P (brimonidine tartrate ophthalmic solution 0.15%), the subject of NDA 21–262 approved March 16, 2001, for the same indication as Alphagan 0.2%. Approval of Alphagan P was based, in part, on references to the safety and efficacy of Alphagan 0.2% and the products' comparability as demonstrated in head-to-head studies. Second, FDA has independently evaluated relevant literature and data for possible postmarketing adverse event reports regarding brimonidine tartrate ophthalmic

solutions, but has found no information that would indicate that Alphagan 0.2% was withdrawn for reasons of safety or effectiveness.

After considering the information contained in the citizen petitions, comments, and agency records, FDA determines that, for the reasons outlined above, brimonidine tartrate ophthalmic solution 0.2% approved under NDA 20–613 was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list Alphagan 0.2% (brimonidine tartrate ophthalmic solution) in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to Alphagan 0.2% (brimonidine tartrate ophthalmic solution) may be approved by the agency.

Dated: 6/4/03
June 4, 2003.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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